a medium, which medium contains antibodies attached to a surface, the binding to the specific microorganism to form an antigen to antibody complex which system comprises:

means for irradiating the medium with laser light in the range of 242-257 nm;

means for sensing the presence of the complex based on the excitation of the nucleic acids of the microorganism in the presence of proportionally very much larger numbers of antibody; and

means for detecting the Raman fingerprint region of the microorganism substantially in the absence of fluorescence.

A3 cont

REMARKS

The Office Action of October 15, 1997 has been received and the comments of the Examiner carefully considered.

In regard to the drawings, upon indication of a Notice of Allowance, formal drawings will be submitted.

The requirement to amend the specification and drawings to reflect that the drawing be identified as Fig. 1 is not believed to be correct. If I identify the **sole** figure of the application as a Fig. 1, this implies that there would be additional figures in the application when there are no additional figures. The Examiner and undersigned attorney may have semantic differences on this specific issue, however, it is believed that they probably could be easily resolved in a telephone call.

Enclosed as a separate sheet with this Amendment is an Abstract.

Claims 1-6 have been rejected under 35 USC §112, second paragraph, as being indefinite for failure to particularly point out and distinctly claim the subject matter Applicant regards as the invention. Claim 1 has been cancelled and re-written as new claim 7. Claim 6 has been cancelled and re-written as new claim 8 It is believed new claims 7 and 8 obviate the rejections regarding claims 1 and 6.

Claims 1-6 have been rejected under 35 USC §112, first paragraph. It is believed in view of new claims 7 and 8 that this rejection is now overcome.

Claims 1-6 have been rejected under 35 USC §103(a) as being unpatentable over Chadha et al. in view of Nelson et al. and either Szoka or Newman.

The Examiner makes the statement on page 10 which goes to the heart of the patentability.

"It would have been obvious to one or ordinary skill in the art to modify the method and system of Chadha, et al., by substituting biospecific antibody for the disclosed polylysine, not only because biospecific antibodies are conventionally used to immobilize bacteria and viral analytes for assay, but also because combining the DNA analytes of Chadha, et al., with the selectivity/specificity of an antigen/antibody immobilization would combine the two most attractive markers for bacterial

identification as suggested by Nelson, et al., thereby resulting in a more efficient identification/detection system and method. No unexpected results are seen. The claimed detection in the presence of an excess of antibody is inherent in the UV resonance enhanced Raman method/spectrograph of Chadha, et al." (Emphasis Added)

The emphasized statements are not valid because what is most expected is an interference from the aromatic components of the antibody. If the resonance Raman method is to be effective in sensitive detection, neither fluorescence interference nor the background resonance Raman interference of the antibody can be present. Both must be essentially absent or significantly suppressed to allow the sensitive detection of the nucleic acid peaks, and specifically the 1485 cm^{-1} peak.

The behavior of the antibody fluorescence is predictable. Fluorescence interference is known not to be a problem with 242 and 521 nm excitation especially. But, the very low intensity and degree of interference of the resonance Raman spectra of the antibody is an unexpected surprise. It is necessary to have a very large excess of antibody used to increase the probability of bacterial capture. If the antibody produces even a tiny percentage of the Raman signal of the bacteria, the bacterial Raman signal will be undetectable against the antibody Raman background, or will require very large amounts of bacteria to overcome this problem. One especially unusual advantage of the claimed method and system is its potential sensitivity as well as speed of detection. Sensitivity will be possible only if the antibody interference is

exceedingly small.

The method of Chadha et al. does suggest that the antibody-bacterial complex will give a DNA resonance Raman signal. The method of Chadha et al. uses polylysine for binding the cells. Polylysine was chosen specifically because it contains no aromatic amino acids which are expected to interfere with the resonance Raman spectra of bacteria. Basically, polylysine was chosen as a binding agent because it is UV resonance Raman silent. Antibodies on the other hand contain significant amounts of aromatic acids which ordinarily produce very significant UV resonance Raman signals which would be expected to interfere with (i.e., reduce the sensitivity of) the DNA Raman signal.

To make a prediction regarding the sensitivity of DNA detection in the presence of an antibody one would have to measure the Raman cross-sections of the relevant modes for bacteria, antibody and the bacteria-antibody complex. At present, none of those data are available.

Aromatic amino acid and nucleic acid data not associated with bacteria, which are known, point toward the region between 242-257 nm to maximize the DNA signal and minimize the protein signal, but protein signals in the 242-257 nm region would not be expected to be negligible or even small on the basis of measured cross-sections. The detection of the DNA Raman signal in the presence of antibody is not a surprise. However, the extent to which the antibody is silent is very surprising and critical to the effective exploitation of the disclosed invention.

Newman teaches that antibody attached to a surface antibody can give rise to an electrical signal proportional to antigen. The invention also takes advantage of the selective formation of antibody-antigen complexes just as does Newman, but all methods such as FIA, RIA, ELISA rely on the basic principles of immunology which are not patented.

The claimed method of detection of the formation of the antibody-bacterial complex is unique, just as Newman's method of detection is unique and patented. The claimed method is more sensitive, by several orders of magnitude.

Szoka uses a labeling method like FIA, RIA and ELISA. It is very different from the disclosed method of detection and the items detected.

Basically, it is Applicants' use of a narrow range of specific UV wavelengths to detect bacterial nucleic acids via Raman spectra sensitively in the presence of antibody which is unique in view of the art. The effects of hypochromism, fluorescence and internal absorption on resonance Raman sensitivities from mixtures make quantitative predictions in this area very difficult at best.

Claim 6 has been rejected under 35 USC §102(b) as being anticipated by Malmqvist et al.

Claim 6 has also been rejected under 35 USC §102(b) as being clearly anticipated by Bogart et al.

Claim 6 has been rejected under 35 USC §102(a-e) as being clearly anticipated by Herron et al.

The above itemized rejections of claim 6 are overcome by now re-written claim 8. The limitations of claim 8 (similar to new claim 7) directed to the excitation of nucleic acids in the presence of proportionately very much large numbers of antibodies are not shown in these references. Accordingly, the arguments set forth above the reasons that claim 6 distinguishes from the art of record are repeated herein in regard to the rejection of original claim 6.

It is believed that to expedite prosecution of the application that a telephone interview would be appropriate. Accordingly, the undersigned requests that the Examiner call the undersigned attorney to discuss the application on the merits prior to issuing any final action.

It is submitted the claims are now in condition for allowance and the same is respectfully requested.

Respectfully submitted,

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